REMARKS

Claims 18, 26-29, 31-69, 71-72, and 73-75, are pending in this application.

Claims 30 and 70, have been cancelled without prejudice or disclaimer.

Claims 26 and 64, have been amended to include the limitations of cancelled claim 30. Further, claim 26 has been amended to include the limitations of cancelled claim 70.

New claim 73 is dependent on claim 26 and recite that "the affinity for antigen binding of the non-cell binding antibody is reduced such that said antibody does not show detectable binding to antigen in ELISAs at 100 times the minium concentration at which binding of the therapeutic antibody is detectable". New claims 74 and 75 further limit the concentration to 1,000 times and 10,000 times, respectively. Support for claims 73-75 appears in the specification at page 22. No new matter has been added.

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments, new claims, and following remarks.

I. At page 2 of the Office Action, the disclosure is objected to because the use of the trademark "campath-1" should be capitalized wherever it appears and should be accompanied by the generic terminology.

In response to the Examiner's objection, Applicants submit that the term "Campath-1" is not a trademark or a trade name. In view of the following, this rejection is respectfully traversed.

The use of the term "Campath-1" antibody as a designation is not indefinite, and is in fact well known to one of ordinary skill in the art. The specification, on page 1, line 27, to page 2, line 2 and lines 10-12, describes Campath-1 as a series of rat monoclonal antibodies which bind to the CD52 antigen which is expressed on the surface of human lymphocytes and monocytes. SEVERAL Applicants note that the Riechmann et al. (Nature 332:323, 1988) reference, cited to the Examiner in IDS No: 5, and relied on by the Examiner in the instant Office Action, states at page 3, line 1:

> There are mAbs to many cell-type-specific differentiation antigens, but only a few have therapeutic potential. Of particular interest is a group of rat mAbs directed against an antigen, the "CAMPATH-1" antigen, which is strongly expressed on virtually all human lymphocytes and monocytes, but is absent from other blood cells including the haemopoietic stem cells[20] . The CAMPATH-1 series contains rat mAb of IgM, IgG2a, and IgG2c isotypes[21], and more recently IgG1 and IgG2b isotypes which were isolated as class-switch variants from the IgG2a-secreting cell line YTH 34.5HL[22] .

The references cited in the above Reichmann et al. passage include: (21) Hale, G., et al. Removal of T cells from Bone Marrow for Transplantation: a Monoclonal Antilymphocyte Antibody that Fixes Human Complement. *Blood* 62, 873-882 (1983); (22) Hale, G., et al. Removal of T Cells from Bone Marrow for Transplantation: Comparison of Rat Monoclonal Antilymphocyte Antibodies of Different Isotypes. *Mol. Biol. Med.* 1, 305-319 (1983); and (22) Hale, G., et al. Isolation of Low-Frequency Class-Switch Variants from Rat Hybrid Myelomas. *J. Immun. Meth.* 103, 59-67 (1987). Enclosed herewith, please find a copy of each of the foregoing references.

The above references further establish that the term "Campath-1" is the accepted terminology in the art for a series of rat mAbs which recognize a human lymphocyte surface antigen. Also, the "Campath-1" antigen has been characterized and designated CD52 as shown by the entry for "Campath-1" in the Encyclopaedia of Immunology, Delves & Roitt (Eds) 402-406 (1998), a copy of which is enclosed.

In view of the remarks set forth above, and the evidence submitted herewith, the term "Campath-1" is not a trademark or trade name, and is in fact a term that is well known and understood by one or ordinary skill in the art, and thus is clear and definite within the meaning of 35 USC § 112, second paragraph. Accordingly, the Examiner is respectfully requested to withdraw this objection.

II. At page 3 of the Office Action, Claims 26-70, have been rejected under 35 USC § 112, second paragraph, as being indefinite.

The Examiner states that the claims are indefinite because they recite that the non-cell binding antibody has reduced affinity (claims 26, 43, and 64), or that the affinity for antigen is reduced to 50%, 10%, or 1% (claims 30-32). The Examiner contends that the exact meaning of the phrases are unclear because it is not clear how a non-cell binding antibody can still have affinity for an antigen. The Examiner questions whether the antibody still binds antigen or not.

Regarding claim 59, the Examiner states that the term "Campath-1" is a trademark or trade name, and as such cannot be properly used in the claim. The Examiner requires that the claim describe the humanized antibody intended.

The term "Campath-1" is not a trademark or trade name, and is in fact a term that is well known and understood by one or ordinary skill in the art, and thus is clear and definite within the meaning of 35 USC § 112, second paragraph. Please see the above remarks presented responsive to the Examiner's objection to the specification. Accordingly, the Examiner is respectfully requested to withdraw this rejection as to claim 59.

Independent claims 26 and 64, have been amended to include the limitations of claim 30. Specifically, claims 26 and 64, have been amended to recite that the affinity of the antibody for the antigen is reduced to 50% or less, of the affinity of the therapeutic antibody. Claim 43 is dependent on claim 26. New dependent claim 73 has been drafted to be dependent on amended claim 26, and further requires that the affinity for antigen binding of the non-cell binding antibody is reduced such that the antibody does not show detectable binding to the antigen in ELISAs at 100 times the minimum concentration at which binding of the therapeutic antibody is detectable. New dependent claims 74 and 75, require 1,000 times and 10,000 times, respectively. New claims 73-75, find support in the specification, at page 22.

The Examiner states that it is not clear how a non-cell binding antibody can still have affinity for an antigen, and that, as a result, the phrases "the affinity for antigen is reduced to 50%" are unclear and indefinite. The Examiner questions whether the antibody still binds antigen or not.

The invention relates to the discovery that a non-cell binding variant of a cell binding therapeutic monoclonal antibody can be used as an effective tolerogen for the therapeutic antibody. The variant antibody is made by modifying one or more amino acid residues involved in antigen binding so that its affinity for the cell-surface antigen is reduced. Preferably, cell-surface binding is effectively lost, hence the term "non-cell binding antibody". However, it is recognized that an antibody variant according to the invention may still have some binding affinity for the cell surface antigen providing the affinity is sufficiently reduced to allow the antibody variant to act as a tolerogen with respect to the therapeutic antibody (please see the specification at page 8, lines 21-25). Binding of modified antibody to antigen may be determined by methods known in the art, such as ELISA as taught on page 21, lines 10-28, of the specification.

The term "non-cell binding antibody" is defined in the specification as an antibody where cell-surface binding is eliminated, or is reduced sufficient to induce tolerance, i.e., where the antibody is an effective tolerogen. This term is defined on page 8, lines 23-26, of the specification. The term "non-cell binding antibody" does not require the total absence of binding. It is noted than an Applicant may be his own lexicographer. Thus, the subject phrases "the affinity for antigen is reduced to 50%", are clear and definite.

Accordingly, it is submitted that claims 26, 43, 64, 73-75, and any claims dependent thereon, as amended or newly presented, are clear and definite within the meaning of 35 USC § 112, second paragraph. Thus, the Examiner is respectfully requested to withdraw this rejection.

III. At page 4 of the Office Action, Claim 59, has been rejected under 35 USC § 112, first paragraph, because the claimed invention is not enabled.

The Examiner states the claimed invention is not enabled because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; or (2) reproducible from the written description. The Examiner states that it is unclear if a cell line which produces an antibody having the exact chemical identity of campath-1 is known and publicly available, or can be reproducibly isolated without undue experimentation. The Examiner suggests depositing the cell line. In view of the following, this rejection is respectfully traversed.

With regard to enablement in the field of monoclonal antibodies, the court in ***In re Wands,*** 858 F.2d 731, 8 USPQ.2d 1400 (Fed. Cir. 1988), found that the PTO erred in rejecting the applicant's claim to immunoassay methods using a specified generic class of antibodies. In this case the applicant deposited a hybridoma cell line that secreted one specific antibody. The court found that the evidence indicated that those skilled in the monoclonal antibody art could, using the state of the art and applicant's written disclosures could, produce and screen other hybridomas secreting other monoclonal antibodies falling within the generic class without undue experimentation. The PTO rejected the generic claims for want of an enabling disclosure. The ***Wands*** court held that enablement is not precluded by the necessity for some experimentation such as routine screening of hybridoma cells that secrete a desired monoclonal antibody from other cells derived from an immunized animal. Further, the ***Wands*** court stated that in the monoclonal antibody art it appears that an "experiment, is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen."

Based on the teachings of the specification and the knowledge in the art, one skilled in the art would clearly be able to practice the claimed invention without undue experimentation.

Further, based on the experimental detail of the production of non-cell binding antibodies or fragments thereof on pages 15-21 of the specification, Applicants submit that the present application is sufficiently detailed to reasonably convey to the skilled artisan, that the inventors, at the time the application was filed, were in possession of the claimed invention.

Regarding deposit of biological materials, the court in ***Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.***, 927 F.2d 1200, 18 USPQ.2d 1016 (Fed. Cir. 1991), held that: "When...the organism is created by insertion of genetic material into a cell obtained from generally available sources, than all that is required is a description of the best mode and an adequate description of the means of carrying out the invention, not deposit of the cells." The ***Wands*** court held that no deposit is necessary if the biological organisms (hybridoma cell lines) can be obtained from readily available sources or derived from readily available starting material through routine screening that does not require undue experimentation. The ***Wands*** court found that the specification provided sufficient support as to method claims because one skilled in the art could using the state of the art and applicant's disclosure, produce and screen other hybridoma cell lines secreting other monoclonal antibodies falling within a generic class, without undue experimentation.

As discussed responsive to the previous rejection and objection, the term "Campath-1" refers to a series of monoclonal antibodies, and thus, no deposit is required. The antibody of the examples has been described in detail (including the sequence) by Riechmann et al., *Nature* 332:323 (1988), and in EP 0328404 A (issued as US Patent No: 5,846,534, "Antibodies to the Antigen Campath-1"). The full sequence of the humanized antibody is also available at: http://www.path.cam.ac.uk/~mrc7/humanisation/seqs/huCD52.html Accordingly, it is known and readily available to the public or obtainable by a reproducible method. In addition, since the claims are not limited to a particular or specific Campath-1 antibody, the deposit requirement does not apply.

In view of the remarks set forth above, the evidence submitted, and the amendments to the claims, it is submitted that the claims adequately teach one of ordinary skill in the art to make and use the invention without undue experimentation, within the meaning of 35 USC § 112, first paragraph. Thus, the Examiner is respectfully requested to withdraw this rejection.

III. At page 5 of the Office Action, Claims 26, 31-32, 54-57, and 63-65, have been rejected under 35 USC 102 (b), as being anticipated by Isaacs et al.

The Examiner states that in view of the Isaacs et al. teaching of a method for producing a non-cell binding antibody that is useful for generating a therapeutic unresponsiveness to the therapeutic antibody, it is inherent since the antibodies have an irrelevant heavy or light chain, that they would not bind antigen thus meeting the reduction of affinity to less than 1%. In view of the amendment to claim 26, this rejection is believed to be overcome.

Claim 26 has been amended to additionally recite that: "and wherein the antibody is not a mixed molecule antibody having an H or L chain of a therapeutic antibody paired with an L or H chain of an unrelated antibody. Thus, Isaacs et al. do not teach each and every element of the claimed invention, as required for anticipation under 35 USC §102 (b). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

III. At page 7 of the Office Action, Claims 26-70, have been rejected under 35 USC 103 (a), as being unpatentable over Isaacs et al., as applied to claims 26, 31-32, 54-56, and 63-65 above, and further in view of Carter et al. and Riechmann et al.

The Examiner states that it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a non-cell binding antibody as taught by Isaacs et al. in view of the well known methods of humanization and alteration in the antigen binding sites of antibodies as taught by Carter et al. and use the Campath-1 antibody as taught by Riechmann et al. The Examiner further states that one of ordinary skill would have

been motivated and have had a reasonable expectation of success to have produced a non-cell binding antibody for inducing therapeutic unresponsiveness to a therapeutic antibody, because Carter teaches well know methods of humanization and alteration in the antigen binding sites of antibodies, and whose methods would result in minimal changes to the humanized antibody to result in reduced antigen binding, because Riechmann et al. teach that a humanized anti-Campath-1 antibody can be used for therapy and to circumvent the anti-globulin response to the Campath-1 antibody, and because Isaacs et al. teach non-binding antibodies for unresponsiveness. A brief analysis of each of the references relied on by the Examiner, is set forth below.

Isaacs et al. teach a method of producing a non-cell binding antibody which is a mixed molecule antibody having an H or an L chain of a therapeutic antibody paired with an L or H chain of an unrelated antibody.

Carter et al. is directed to methods for the efficient humanization of antibodies "so as to retain or improve the affinity of the non-human donor antibody for a given antigen". Please see col. 4, lines 30-35, of Carter et al. The disclosed method involves identifying the CDR's of the donor antibody and importing the CDRs into the human acceptor antibody; and identifying amino acid residues in the Framework. Region (FR) of the donor antibody which is non-homologous to the consensus antibody and could reasonably be expected to influence antigen binding and substituting that residue for the corresponding amino acid residue in the consensus antibody FR sequence.

Reichmann et al. describe the construction of a humanized Campath-1 antibody, as discussed herein and in the specification.

In the present case, the invention is directed to a method of producing a non-cell binding antibody, where the method includes identifying the amino acid residues of a therapeutic antibody which are involved in antigen binding and modifying the residues where the non-cell binding antibody has reduced affinity for the antigen and includes at least one epitope which induces an immune response and induces immunological tolerance to the therapeutic antibody (as

summarized in item 11, at pages 5-6 of the instant Office Action) and where the antibody is not a mixed molecule antibody having an H or L chain of a therapeutic antibody paired with an L or H chain of an unrelated antibody, as required by claim 26. It is the present inventors who have surprisingly discovered that with Campath-1H, cell binding could be eliminated or significantly reduced, i.e., tolerance induced, using a limited set of mutations (1 or 2).

Regarding claims 26-70, it is submitted that the Examiner has not established a proper case of *prima facie* obviousness. A proper case of *prima facie* obviousness under 35 U.S.C.§103, requires that the prior art as a whole, must suggest the desirability of making the claimed combination and provide a reasonable expectation of success. See ***In re Dow Chemical Co.***, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir.1988).

The ***Dow*** court further held that "In determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention." The court in ***In re Gurley***, 27 F.3d 551, 31 USPQ2d 1130 (Fed. Cir.1994), held that "A prior art reference may be said to *teach away* when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in

the reference, or would be led in a direction divergent from the path that was taken by the applicant." The court in ***Busch & Lamb, Inc. v. Barnes-Hind/Hydro curve, Inc.***, 796 F.2d 443, 230 USPO 416 (Fed. Cir.1986), held that "A reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered." Further, it is noted that "obvious to try" is not a proper standard for obviousness. The court in ***In re Lilly & Co.***, 902 F.2d 943, 14 USPQ.2d 1741 (Fed. Cir.1990), held that an "obvious-to try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be

obtained if certain directions were pursued." Further, the court in ***ATD Corp. v. Lydall, Inc***, 159 F.3d 534, 48 USPO.2d 1321 (Fed. Cir. 1998), held that "There must be a teaching or suggestion within the prior art...to select particular elements, and to combine them in the way they were combined by the inventor."

In the present case, none of Isaacs et al., Carter et al., or Riechmann et al., taken alone or together, suggest the desirability of modification of the respectively disclosed antibodies or methods of making them, to achieve the claimed method for producing a non-cell binding antibody for inducing immunological tolerance to a therapeutic antibody.

Moreover, none of the references taken alone or together suggest modification of a therapeutic antibody to effect removal of binding ability, let alone modification of any such antibody to achieve the claimed invention. Rather, all of the references relied on by the Examiner, teach methods of modifying antibodies such that binding is ***maximized*** while the immunogenic response to the modified antibody is lessened by "humanizing" modification.

In fact, Isaacs et al. ***teach away*** from the production and use of a non-mixed, non-cell binding molecule variants as a means for inducing tolerance. Isaacs et al. teach on page 310, col. 1, lines 14 to 18, that: "There was no special advantage for tolerance induction of using non-cell binding variants of the therapeutic mAb itself (HK, GL) over an isotyped matched Ig (CAMPATH 1-g), in this particular situation."

In the remainder of the discussion, Isaacs et al. discuss theoretical use of mixed molecule, non-binding, antibodies in tolerance induction, concluding that: "It may be seen that, in practice, we can never completely match the spectrum of immunogenic peptides derived from a therapeutic mAb via non-binding variants"

The above passage is limited solely to the use of mixed molecule variants (HK and GL), and does not even remotely suggest the possibility of using non-mixed molecule therapeutic antibody variants. The passage ***teaches away*** from further investigation of such mixed variants because as stated, in practice, suitable matching is never expected to be achieved. Also, Isaacs et

al. require the use of a two-stage tolerazation process where two antibodies (HK and GL) were required to induce tolerance. The present inventors have overcome this problem by providing a system which requires a single antibody.

Thus, one of ordinary skill in the art in view of Isaacs et al. would be led away from investigating non-binding variants, let alone non-mixed, non-cell binding variants, as required by the present claims. Nor would the skilled artisan be motivated to investigate the use of such variants to induce tolerance.

Regarding Carter et al., and Riechmann et al., these references are directed to maximizing binding affinity to humanized forms of rodent antibodies. The CDRs are the expected mediators of antibody specificity. However, neither Carter et al., nor Riechmann et al., suggest altering CDRs to ***reduce*** binding affinity. It is the present inventors who have discovered how to minimize binding effectiveness of the non-cell binding antibody while maximizing the identity between the non-cell binding antibody and the therapeutic antibody to enable the non-cell binding antibody to effectively induce tolerance to the therapeutic antibody.

Thus, one of ordinary skill in the art, faced with the problem of producing a non-cell binding antibody where binding is eliminated or sufficiently reduced would have no reason or motivation, to look to references directed to methods of modifying antibodies such that binding is maximized.

Assuming *arguendo*, one of ordinary skill in the art was motivated to produce a non-cell binding antibody, there is no teaching, suggestion, or guidance provided, in any of the references taken alone or together, as to the nature or extent of the modifications that might be needed in order to reduce affinity to the point where cell-binding is effectively lost. For example, alteration of too may residues in CDRs could mean that the variant produced might tolerise to itself, but would not tolerise to the native peptides encompassing the corresponding CDRs of the therapeutic antibody. The combination of references, at most show that it may have been "obvious to try." It is noted that an "obvious-to try" situation exists when a general disclosure

may pique a scientist's curiosity, such that further investigation might be done, but does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.

It is submitted that one of ordinary skill in the art, in view of the cited references, would not have any motivation to eliminate binding by modifying CDRs, and would have no reasonable expectation of success since the references provide no guidance: (1) as to how many changes in the CDRs would be needed, (2) as to the key residues involved in binding, and (3) as to what combinations would be expected to be successful. Again, it is the present inventors who have surprisingly discovered that binding can be eliminated with a limited set of mutations.

In view of the arguments set forth above, the amendments to the claims, and the evidence submitted herewith, it is submitted that the Examiner has not established a proper case of *prima facie* obviousness, and further that nothing in the cited references, taken alone or together, render the claimed invention obvious within the meaning of 35 USC § 103 (a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

In view of the foregoing amendments, new claims, and remarks, it is respectfully submitted that the application is in condition for allowance. Such allowance is solicited.

Attached hereto is a marked-up version of the changes made to claim 26, by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

If the Examiner has any questions regarding this amendment, the application in general, or has any suggestions for placing the application in condition for allowance, the Examiner is requested to call the undersigned at the number listed below.

Respectfully submitted,

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Version with markings to show changes made

26. (Amended) A method of producing a non-cell binding antibody for inducing immunological tolerance to a therapeutic antibody having affinity for a cell-surface antigen, said method comprising:

identifying one or more amino acid residues of the therapeutic antibody which are involved in antigen binding, and

modifying on or more of the identified amino acid residues of the therapeutic antibody to obtain the non-cell binding antibody,

wherein the non-cell binding antibody (1) has [reduced affinity for antigen binding] affinity for antigen binding of the non-cell binding antibody reduced to 50% or less as compared to said therapeutic antibody due to modification(s), (2) comprises at least one epitope present in the therapeutic antibody which induces an immune response, and (3) induces immunological tolerance to the therapeutic antibody, and

wherein said non-cell binding antibody is not a mixed molecule antibody having an H or L chain of a therapeutic antibody paired with an L or H chain or an unrelated antibody.

64. (Amended) A method of producing a non-cell binding antibody fragment for inducing immunological tolerance to a therapeutic antibody having affinity for a cell-surface antigen, said method comprising:

fragmenting the therapeutic antibody to obtain said non-cell binding antibody fragment,

said non-cell binding antibody fragment (1) having [reduced] affinity for antigen binding of the non-cell binding antibody reduced to 50% or less as compared to said therapeutic antibody due to said fragmentation, (2) comprising at least one epitope present in the therapeutic antibody which induces an immune response, and (3) inducing immunological tolerance to the therapeutic antibody.